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Chronic kidney disease and vitamin D: how much is adequate?

Marco Ruggiero[1] and Stefania Pacini[2]

Mehrotra *et al.* demonstrate that there still is hypovitaminosis D in adults with chronic kidney disease (CKD) in the United States, and this defect is associated with increased risk for death. Definition of the adequate amount of vitamin D, however, is still uncertain; polymorphisms of the gene encoding the vitamin D receptor might be responsible for this uncertainty. People carrying less efficient variants of the receptor might need higher amounts of vitamin D.

Kidney International (2009) **76,** 931–933. doi:10.1038/ki.2009.312

In trying to study the relationships between vitamin D and chronic kidney disease (CKD), the nephrologist might feel like Achilles in the footrace with the tortoise of Zeno's famous paradox ('In a race, the quickest runner can never overtake the slowest, since the pursuer must first reach the point whence the pursued started, so that the slower must always hold a lead'[1]). In fact, at the time of the writing of this article, a quick search for the two key words 'vitamin D' and 'CKD' in PubMed (www.pubmed.gov) yielded 2529 articles; studying four articles a day (that is, one hour of peaceful study a day, every day: a dream, for most of us!), it would take 632 working days to be updated in the matter—more than two years—and, in the meantime, tens or hundreds of new articles would have been published.

It has become evident that the amount of available scientific information is greater than our ability to process it, and we too, as scientists, envisage a prophetic sense in the words of an old song of The Police (1981): 'Too much information running through my brain; too much information, driving me insane.' Thus, articles such as that of Mehrotra *et al.*,[2] published in this issue, are a welcomed contribution to the field, because such vast and comprehensive studies distill solid information that can be useful both in daily practice and as a starting point for further research. In fact, the article by Mehrotra *et al.*[2] can be considered as a meta-analysis of data gathered from a large cohort (more than 3000 subjects) of adults with CKD enrolled in the Third National Health and Nutrition Examination Survey (NHANES III)—a random sampling of community-dwelling individuals in the United States conducted between 1988 and 1994. The results are impressive and confirm beyond any possible doubt something that many in the field had suspected for a long time: there still is hypovitaminosis D in adults with CKD in the United States, and this defect is associated with increased risk for death. As with every other association study, a cause–effect relationship cannot be traced, but the message is clear, and it directly points to the question recently addressed in this journal, 'How much vitamin D should we prescribe?'[3]

Indeed, the definition itself of hypovitaminosis D is a tricky business: the fact that rickets is no longer a major public-health problem in Western countries, as it was in the 1930s, does not mean that we are consuming enough vitamin D. Apparently the problems with vitamin D began a long time ago: as civilization and the industrial revolution enabled humans to work indoors and to wear more clothes when in the sun, these cultural changes reduced natural production of vitamin D and caused deficiency diseases. Because of this, in many countries, foods such as milk, yogurt, margarine, oil spreads, breakfast cereal, pastries, and bread are 'fortified' with vitamin D_2 and/or vitamin D_3, to minimize the risk of vitamin D deficiency.[4] In the United States and Canada, for example, fortified milk typically provides 100 IU per glass, or one-quarter of the estimated adequate intake for adults over the age of 50. Today, adequate intake is defined as 200 IU per day from infancy to age 50, 400 IU per day for ages 51–70, and 600 IU per day for ages over 70. The 100% daily value used for product labels is 400 IU. The practical reality, however, is that, on average, the diet in the United States provides only 100 IU per day. But to which condition does the adjective 'adequate' refer? (Figure 1).

Just to remember how fluid the scenario is, it is worth noting that, today, no one is sure what 'adequate' truly means.

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Figure 1 | Vitamin D and tortoises. Vitamin D_3 is considered safe at about 100 IU/kg/wk in reptiles such as these tortoises (from the 89th plate of Ernst Haeckel's *Kunstformen der Natur* (1904), depicting organisms classified as *Chelonia*). In humans, however, the adequate amount of vitamin D supplementation has yet to be determined.

In fact, the Institute of Medicine of the National Academies of the United States is revisiting vitamin D and calcium recommendations. A committee to review dietary reference intakes for vitamin D and calcium has been established; the second committee meeting was held 4–5 August 2009 (http://www.iom.edu/?id=68400) in Washington, DC , and the final report is expected in the spring of 2010. The need to revisit existing values stems from the fact that vitamin D (and its deficiency) has been associated with a variety of diseases ranging from cancer to osteoporosis, from cardiovascular to autoimmune diseases. And it is quite possible that the adequate amount to prevent rickets is not the same as that to prevent cancer.

When it comes to hypovitaminosis D–associated all-cause mortality, the issue is obviously even more complex, as Mehrotra *et al.*[2] correctly point out; and even though the authors could not go down to the molecular level using the data of NHANES III, it could be hypothesized that the gene coding for the receptor of vitamin D might provide some answers to this puzzle. In this particular footrace, Dr. Achilles might easily overtake the tortoise receptor: in 55 working days, all the 222 articles dealing with vitamin D receptor (VDR) and CKD could be read. And the articles dealing with VDR gene polymorphisms and CKD are only 16—less than one morning of peaceful reading.

Just like any other hormone, vitamin D exerts its effects through interaction with a receptor protein, in this case a ligand-activated nuclear receptor that in turn controls the transcription of a large number of genes. The VDR gene shows a variety of individual polymorphisms that were first demonstrated to be associated with bone turnover and density. However, as vitamin D became associated with other conditions, VDR gene polymorphisms also were linked to several common diseases, including those that might account for all-cause mortality in CKD patients, such as cardiovascular disease, diabetes, and cancer. But unlike vitamin D itself, VDR gene polymorphisms have been associated also with the pathogenesis of CKD, as if some polymorphisms (in particular, the one evidenced by the *Fok*I restriction enzyme) were involved in the onset of renal failure.[5] This adds complexity to an already complex issue; here we have a vitamin whose deficiency is associated with mortality in CKD patients, and a receptor whose variations (due to gene polymorphism) are associated both with the onset of CKD and with death-causing diseases.

Since our human minds force us to simplify things in order to identify foreseeable patterns, a simple scheme could be as follows. When vitamin D is adequate and its receptor works well, no major problem should arise, either in the general population or in CKD patients; all the other combinations are associated with problems. And if we want to find an oversimplified common denominator for these problems, inflammation could be a candidate. In fact, chronic inflammation plays an important role in the pathogenesis of cardiovascular disease in uremic patients, and administration of vitamin D analogues provides cardiovascular benefit in dialysis patients.[6] The link between vitamin D and chronic inflammation could be found in the immunomodulatory effects of vitamin D, which activates monocytes, stimulates cell-mediated immunity, and suppresses lymphocyte proliferation.[7]

From these few considerations on the receptor, it follows that, when we take into account its polymorphisms, we are forced to use a more 'molecular' (or functional) definition of 'adequate' that has to be based on the efficiency of the receptor in controlling target genes. In fact, it has been known for years that, because of gene polymorphism, certain variants of the receptor are less efficient than others in transducing

the vitamin D signal;[8] for people carrying these less efficient receptors, the adequate amount of vitamin D supplementation could be higher. Therefore, it is easy to forecast that determination of adequate supplementation of vitamin D according to genotype (both in the general population and in CKD patients) will be a demanding challenge for the immediate future. Although we might not be as fundamentalist as those who maintain that vitamin D makes the world go round,[9] we are certain that we shall not run out of articles to read any time soon; and the article by Mehrotra *et al.*[2] is a good starting point.

The final words of their discussion—'Randomized trials are warranted…'[2]—are routinely found at the end of scientific papers, but in this case they have to be considered an easy prophecy. Dr Achilles is not supposed to ever catch the tortoise, and from a quantum mechanics point of view, Zeno was ultimately right.[10]

DISCLOSURE
The authors declared no competing interests.

ACKNOWLEDGMENTS
University of Firenze, Progetto di Ricerca di Ateneo provided financial support.

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